



HEPATITIS C May 2003

- 1: Sevastianos VA, Deutsch M, Dourakis SP, Manesis EK.
Pegylated interferon-2b-associated autoimmune thrombocytopenia in a patient with chronic hepatitis C.
Am J Gastroenterol. 2003 Mar;98(3):706-7. No abstract available.
PMID: 12650821 [PubMed - indexed for MEDLINE]
- 2: Fujita N, Kaito M, Takeo M, Iwasa M, Ikoma J, Watanabe S, Adachi Y.
Nonimmune complexed HCV RNA titer in serum as a predictor of interferon response in patients with chronic hepatitis C.
Am J Gastroenterol. 2003 Mar;98(3):645-52.
PMID: 12650801 [PubMed - indexed for MEDLINE]
- 3: Shehab TM, Orrego M, Chunduri R, Lok AS.
Identification and management of hepatitis C patients in primary care clinics.
Am J Gastroenterol. 2003 Mar;98(3):639-44.
PMID: 12650800 [PubMed - indexed for MEDLINE]
- 4: Chong CA, Gulamhussein A, Heathcote EJ, Lilly L, Sherman M, Naglie G, Krahn M.
Health-state utilities and quality of life in hepatitis C patients.
Am J Gastroenterol. 2003 Mar;98(3):630-8.
PMID: 12650799 [PubMed - indexed for MEDLINE]
- 5: Liu J, Manheimer E, Tsutani K, Gluud C.
Medicinal herbs for hepatitis C virus infection: a Cochrane hepatobiliary systematic review of randomized trials.
Am J Gastroenterol. 2003 Mar;98(3):538-44. Review.
PMID: 12650784 [PubMed - indexed for MEDLINE]
- 6: Arguedas MR, Chen VK, Eloubeidi MA, Fallon MB.
Screening for hepatocellular carcinoma in patients with hepatitis C cirrhosis: a cost-utility analysis.
Am J Gastroenterol. 2003 Mar;98(3):679-90.
PMID: 12650806 [PubMed - indexed for MEDLINE]
- 7: Guido M, Bortolotti F, Leandro G, Jara P, Hierro L, Larrauri J, Barbera C, Giacchino R, Zancan L, Balli F, Crivellaro C, Cristina E, Pucci A, Rugge M.
Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time?
Am J Gastroenterol. 2003 Mar;98(3):660-3.
PMID: 12650803 [PubMed - indexed for MEDLINE]

8: Mayo MJ.

Extrahepatic manifestations of hepatitis C infection.
Am J Med Sci. 2003 Mar;325(3):135-48. Review.
PMID: 12640289 [PubMed - indexed for MEDLINE]

9: Anders RA, Yerian LM, Tretiakova M, Davison JM, Quigg RJ, Domer PH, Hoberg J, Hart J.

cDNA microarray analysis of macroregenerative and dysplastic nodules in end-stage hepatitis C virus-induced cirrhosis.
Am J Pathol. 2003 Mar;162(3):991-1000.
PMID: 12598331 [PubMed - indexed for MEDLINE]

10: Pellegrino A, de Capriles CH, Magaldi S, Montes de Oca I, Ruiz ME, Perez C, Mata-Essayag S.

Case report: severe juvenile type paracoccidioidomycosis with hepatitis C.
Am J Trop Med Hyg. 2003 Mar;68(3):301-3.
PMID: 12685634 [PubMed - indexed for MEDLINE]

11: Squires SG, MacDonald DM, Scott JW, Anderson DR, Peltekian K.
[Evaluation of Nova Scotia's hepatitis C risk notification program.]

Can Commun Dis Rep. 2003 Apr 1;29(7):61-5. No abstract available.
PMID: 12693272 [PubMed - indexed for MEDLINE]

12: Hogg RS, Craib KJ, Pi D, Lee SS, Minuk GY, Shapiro CM, Schechter MT, O'Shaughnessy MV.

Health and socioeconomic status differences among antibody hepatitis C positive and negative transfusion recipients, 1986-1990.
Can J Public Health. 2003 Mar-Apr;94(2):130-4.
PMID: 12675170 [PubMed - indexed for MEDLINE]

13: Zou S, Forrester L, Giulivi A.

Hepatitis C update.
Can J Public Health. 2003 Mar-Apr;94(2):127-9. No abstract available.
PMID: 12675169 [PubMed - indexed for MEDLINE]

14: Clin Chem 2003 Mar;49(3):450-4

Validation of the FibroTest biochemical markers score in assessing liver fibrosis in hepatitis C patients.

Rossi E, Adams L, Prins A, Bulsara M, de Boer B, Garas G, MacQuillan G, Speers D, Jeffrey G.

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BACKGROUND: Determining the stage of fibrosis by liver biopsy is important in managing patients with hepatitis C virus infection. We investigated the predictive value of the proprietary FibroTest score to accurately identify significant fibrosis in Australian hepatitis C patients. METHODS: Serum obtained from 125 confirmed hepatitis C patients before antiviral therapy was analyzed for haptoglobin, alpha(2)-macroglobulin, apolipoprotein A1, bilirubin, and gamma-glutamyltransferase activity, and the FibroTest score was computed. Liver fibrosis pathology was staged according to a defined system on a scale of F0 to F4. We used predictive values and a ROC curve to assess the accuracy of FibroTest scores. RESULTS: The prevalence of significant fibrosis defined by liver biopsy was 0.38. The most useful single test for predicting significant fibrosis was serum alpha(2)-macroglobulin (cutoff value, 2.52 g/L; sensitivity, 75%; specificity, 67%). The negative predictive value of a FibroTest score <0.1 was 85%, and the positive predictive value of a score >0.6 was 78%.

Although 33 of the 125 patients had FibroTest scores <0.1 and were therefore deemed unlikely to have fibrosis, 6 (18%) had significant fibrosis. Conversely, of the 24 patients with scores >0.6 who were likely to have significant fibrosis, 5 (21%) had mild fibrosis. Of the 125 patients in the cohort, 57 (46%) could have avoided liver biopsy, but discrepant results were recorded in 11 of those 57 (19%).

CONCLUSION: The FibroTest score could not accurately predict the presence or absence of significant liver fibrosis.

PMID: 12600957 [PubMed - indexed for MEDLINE]

15: Clin Infect Dis 2003 Apr 15;36(8):1086-7

Comment on:

Clin Infect Dis. 2002 Oct 1;35(7):873-9.

J Infect Dis. 2000 Jun;181(6):2033-6.

Hepatitis C viremia persistently suppressed by HAART.

Ranieri R, Santambrogio C, Veronelli A, Pontiroli AE.

PMID: 12684926 [PubMed - indexed for MEDLINE]

16: Clin Infect Dis 2003 Apr 15;36(8):1039-46

Testing, referral, and treatment patterns for hepatitis C virus coinfection in a cohort of veterans with human immunodeficiency virus infection.

Fultz SL, Justice AC, Butt AA, Rabeneck L, Weissman S, Rodriguez-Barradas M; VACS-3 Project Team.

Center for Health Equity Research and Promotion, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

We examined testing, referral, and treatment of patients with hepatitis C among HIV-infected patients in the Veterans Aging 3-Site Cohort Study by using patient- and provider-completed surveys and laboratory, pharmacy, and administrative records from the Department of Veterans Affairs electronic medical record. Of 881 human immunodeficiency virus-positive patients, 43% were coinfecting with hepatitis C virus. Of these, 88 (30%) reported current alcohol consumption. Only one-third were counseled to reduce or stop alcohol consumption. Coinfected patients with indications for hepatitis C treatment had a high rate of contraindications, including both medical and psychiatric comorbidities. Of the 65 patients with indications for hepatitis C therapy and free of contraindications for treatment, only 18% underwent liver biopsy and 3% received IFN. Although treatment indications are common in this population, contraindications are also common. Health care providers are often unaware of alcohol consumption that may accelerate the course of hepatitis C, increase the risk of hepatocellular carcinoma, and reduce treatment efficacy.

PMID: 12684917 [PubMed - indexed for MEDLINE]

17: Eur J Neurol 2003 Mar;10(2):183-5

Motor-axonal polyneuropathy associated with hepatitis C virus.

Costa J, Resende C, de Carvalho M.

Department of Neurology, Hospital de Santa Maria, Lisbon, Portugal.

The association between hepatitis C virus (HCV) infection, the presence of mixed cryoglobulinemia and peripheral neuropathy is well-documented (Apartis et al., 1996). HCV is the chief cause of essential mixed cryoglobulinemia (type II cryoglobulinemia) with cryoglobulins present in up to half of patients with HCV infection (Akriviadis et al., 1997). More recently it has been stated that peripheral polyneuropathy may be associated with HCV chronic infection without mixed cryoglobulinemia (Lidove et al., 2001). Patients usually present with a clinical and electrophysiology--predominantly sensory axonopathies (Apartis et al., 1996; Heckmann et al., 1999) or less frequently with fulminating vasculitis and mononeuropathy multiplex syndrome (David et al., 1996)--especially when

associated with cryoglobulinemia. We report, for the first time, the association between pure motor-axonal polyneuropathy and HCV infection without cryoglobulinemia.

PMID: 12603295 [PubMed - indexed for MEDLINE]

18: Eur J Surg Oncol 2003 Apr;29(3):266-71

Hepatitis viral status affects the pattern of intrahepatic recurrence after resection for hepatocellular carcinoma.

Wakai T, Shirai Y, Yokoyama N, Nagakura S, Hatakeyama K.

Division of Digestive and General Surgery, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.

AIM: To define whether the patterns of intrahepatic recurrence after resection for hepatocellular carcinoma differ according to hepatitis viral status. METHODS: One hundred and eleven patients undergoing a curative resection for hepatocellular carcinoma were divided into three groups: the C-viral group (n=55), which tested positive for hepatitis C antibody; the B-viral group (n=32), which tested positive for hepatitis B surface antigen; and the non-B non-C (NBNC) group (n=24), which tested negative for both hepatitis B surface antigen and hepatitis C antibody. The long-term outcomes were analyzed retrospectively. RESULTS: The pattern of development of intrahepatic recurrence differed between the NBNC group and the other groups: the cumulative probability of intrahepatic recurrence reached a plateau at 2.4 years after resection in the NBNC group, while it continued to increase steadily in the hepatitis viral groups. The C-viral group showed a higher incidence of intrahepatic recurrence than the other groups by univariate ($P=0.0306$) and multivariate (relative risk=1.69, $P=0.0429$) analyses. Multiple intrahepatic recurrent lesions were more common in the C-viral group ($P=0.0457$). CONCLUSIONS: Multicentric carcinogenesis in the remnant liver was less common in the NBNC group than in hepatitis viral groups. Hepatitis C virus infection is a significant risk factor for intrahepatic recurrence after resection and is also associated with multiple intrahepatic recurrent lesions.

PMID: 12657238 [PubMed - indexed for MEDLINE]

19: Gastroenterology 2003 Apr;124(4):1166-7

Comment on:

Gastroenterology. 2002 May;122(5):1303-13.

Optimal IFN therapy for 40-year-old patients with severe HCV-1b infection.

Moriguchi H, Kobayashi M, Chung RT, Sato C.

Publication Types:

Comment

Letter

PMID: 12671922 [PubMed - indexed for MEDLINE]

20: Gastroenterology 2003 Mar;124(3):867-8

High frequency of CCR5-delta32 homozygosity in HCV-infected, HIV-1-uninfected hemophiliacs results from resistance to HIV-1.

Zhang M, Goedert JJ, O'Brien TR.

Publication Types:

Letter

PMID: 12612937 [PubMed - indexed for MEDLINE]

21: Gastroenterology 2003 Mar;124(3):868-9; author reply 869-70

Comment on:

Gastroenterology. 2002 Jun;122(7):1721-8.

HCV chronic infection and CCR5-delta32/delta32.

Mangia A, Santoro R, D'agruma L, Andriulli A.

Publication Types:

Comment

Letter

PMID: 12612938 [PubMed - indexed for MEDLINE]

22: Gut 2003 Mar;52(3):425-32

Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C.

Siebert U, Sroczynski G, Rossol S, Wasem J, Ravens-Sieberer U, Kurth BM, Manns MP, McHutchison JG, Wong JB; German Hepatitis C Model (GEHMO) Group.; International Hepatitis Interventional Therapy (IHIT) Group. Harvard Center for Risk Analysis, Harvard School of Public Health, Boston, MA, USA.

BACKGROUND: Peginterferon alpha-2b plus ribavirin therapy in previously untreated patients with chronic hepatitis C yields the highest sustained virological response rates of any treatment strategy but is expensive. **AIMS:** To estimate the cost effectiveness of treatment with peginterferon alpha-2b plus ribavirin compared with interferon alpha-2b plus ribavirin for initial treatment of patients with chronic hepatitis C. **METHODS:** Individual patient level data from a randomised clinical trial with peginterferon plus ribavirin were applied to a previously published and validated Markov model to project lifelong clinical outcomes. Quality of life and economic estimates were based on German patient data. We used a societal perspective and applied a 3% annual discount rate. **RESULTS:** Compared with no antiviral therapy, peginterferon plus fixed or weight based dosing of ribavirin increased life expectancy by 4.2 and 4.7 years, respectively. Compared with standard interferon alpha-2b plus ribavirin, peginterferon plus fixed or weight based dosing of ribavirin increased life expectancy by 0.5 and by 1.0 years with incremental cost effectiveness ratios of 11,800 euros and 6600 euros per quality adjusted life year (QALY), respectively. Subgroup analyses by genotype, viral load, sex, and histology showed that peginterferon plus weight based ribavirin remained cost effective compared with other well accepted medical treatments. **CONCLUSIONS:** Peginterferon alpha-2b plus ribavirin should reduce the incidence of liver complications, prolong life, improve quality of life, and be cost effective for the initial treatment of chronic hepatitis C.

Publication Types:

Clinical Trial

Multicenter Study

Randomized Controlled Trial

PMID: 12584228 [PubMed - indexed for MEDLINE]

23: Gut 2003 Mar;52(3):404-9

Thrombotic risk factors and extent of liver fibrosis in chronic viral hepatitis.

Papatheodoridis GV, Papakonstantinou E, Andrioti E, Cholongitas E, Petraki K, Kontopoulou I, Hadziyannis SJ.

Hippokration General Hospital, Athens, Greece.

BACKGROUND AND AIMS: Thrombosis of the small intrahepatic veins has been suggested to trigger liver tissue remodelling. We evaluated the prevalence of multiple thrombotic risk factors and their association with the extent of fibrosis in chronic viral hepatitis. **METHODS:** Ninety consecutive patients with chronic hepatitis B or C without malignancy, a history of venous thrombosis, or antiviral/immunosuppressive therapy within the last six months were included. Thrombophilic and coagulation factors were evaluated on the liver biopsy day. **RESULTS:** One or more thrombotic risk factors were found in 68% and ≥ 2 factors in 37% of patients. Higher necroinflammatory activity was independently associated with higher prothrombin time ($p=0.003$), alanine aminotransferase level ($p=0.011$), and histological staging ($p=0.018$). Patients with staging scores of 4-6 compared with those with scores of 0-3 more frequently had deficiency of protein C

(24% v 3%; p=0.007), antithrombin III (28% v 5%; p=0.005), and plasminogen (19% v 2%; p=0.03), and a trend for more frequent activated protein C resistance (8% v 0%; p=0.075). The presence of > or =1 significant thrombotic risk factor was observed in 11/25 (44%) patients with staging scores of 4-6 and in 6/65 (9%) patients with scores of 0-3 (p<0.001), being the only variable independently associated with advanced staging (odds ratio 2.4, p=0.02). CONCLUSIONS: Thrombotic risk factors are frequently detected in patients with chronic viral hepatitis and the presence of > or =1 significant factor is associated with more advanced fibrosis. Whether the association of such thrombophilic conditions with advanced fibrosis is a primary or secondary phenomenon and whether their development in combination with local inflammation accelerate the progression of liver fibrosis need further evaluation.
PMID: 12584224 [PubMed - indexed for MEDLINE]

24: Hepatology 2003 Apr;37(4):781-7

Primary lymphoma of the liver: clinical-pathological features and relationship with HCV infection in French patients.

Bronowicki JP, Bineau C, Feugier P, Hermine O, Brousse N, Oberti F, Rousselet MC, Dharancy S, Gaulard P, Flejou JF, Cazals-Hatem D, Labouyrie E.

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Primary lymphoma of the liver (PLL) is rare. In some cases, the hepatic lymphoma has been diagnosed in patients who were infected by the hepatitis C virus (HCV). It has been suggested that HCV plays a role in the pathogenesis of lymphoma. The aim of our multicentric retrospective study was to assess the characteristics of PLL and to determine the prevalence of HCV infection in PLL. Thirty-one immunocompetent patients (anti-human immunodeficiency virus, anti-human T-cell leukemia/lymphoma virus negative, no history of allograft) with PLL fulfilled the entire selection criteria.

The liver biopsy specimens were reassessed by the same pathologist. The non-Hodgkin's lymphomas were classified according to the World Health Organization classification. Blood samples were tested in 28 patients for antibodies to HCV, and HCV RNA was detected by reverse transcription polymerase chain reaction. In the majority of cases, the clinical, biologic, and radiologic data were nonspecific. Twenty-seven of 31 patients presented a B-cell lymphoma corresponding to the centroblastic morphologic variant of a diffuse, large B-cell lymphoma (22 cases), a Burkitt's lymphoma (1 case), an extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (3 cases), and unclassified, small B-cell lymphoma (1 case). The 4 other cases were T-cell lymphomas. The prevalence of HCV infection was 21% (6 of 28 cases). All of these patients were positive for HCV RNA by polymerase chain reaction in blood. Most of the HCV-infected patients presented a high-grade, B-cell type lymphoma. In conclusion, our study confirms the rarity of PLL and demonstrates an increased prevalence of HCV infection.

PMID: 12668970 [PubMed - indexed for MEDLINE]

25: Hepatology 2003 Apr;37(4):949-50; author reply 950

Comment on:

Hepatology. 2002 Nov;36(5):1273-9.

Threshold for neutropenia in the adjustment of interferon treatment in HCV infection. Renou C, Harafa A, Cummins C, Muller P, Demattei C, Jouve E, Bertrand JJ, Halfon P. Publication Types:

Comment

Letter

PMID: 12668993 [PubMed - indexed for MEDLINE]

26: Hepatology 2003 Apr;37(4):950-1; author reply 951

Comment on:

Hepatology. 2002 Oct;36(4 Pt 1):973-7.

Prediction of histology in hepatitis C.

Puoti C, Castellacci R, Montagnese F, Bellis L, Festuccia F, Corvisieri P.

Publication Types:

Comment

Letter

PMID: 12668994 [PubMed - indexed for MEDLINE]

27: Hepatology 2003 Apr;37(4):788-94

The relationship of in vivo ³¹P MR spectroscopy to histology in chronic hepatitis C.

Lim AK, Patel N, Hamilton G, Hajnal JV, Goldin RD, Taylor-Robinson SD.

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Liver biopsy remains the gold standard for characterizing diffuse liver disease and is associated with significant morbidity and, rarely, mortality. Our aim was to investigate whether a noninvasive technique, in vivo phosphorus 31 ((³¹P)-magnetic resonance spectroscopy (MRS), could be used to assess the severity of hepatitis C virus (HCV)-related liver disease. Fifteen healthy controls and 48 patients with biopsy-proven HCV-related liver disease were studied prospectively. Based on their histologic fibrosis (F) and necroinflammatory (NI) scores, patients were divided into mild hepatitis (F \leq 2/6, NI \leq 3/18), moderate/severe hepatitis (3 \leq F \leq 6 or NI \geq 4/18), and cirrhosis (F = 6/6). Hepatic (³¹P) MR spectra were obtained using a 1.5-T spectroscopy system. Quantitation of the (³¹P) signals was performed in the time domain using the Advanced MAgnetic RESonance algorithm. There was a monotonic

increase in the mean \pm 1 standard error phosphomonoester (PME) to phosphodiester (PDE) ratios for the control, mild disease, moderate disease, and cirrhosis groups: 0.15 \pm 0.01, 0.18 \pm 0.02, 0.25 \pm 0.02, 0.38 \pm 0.04, respectively (ANOVA, P \leq .001). An 80% sensitivity and specificity was achieved when using a PME/PDE ratio less than or equal to 0.2 to denote mild hepatitis and a corresponding ratio greater than or equal to 0.3 to denote cirrhosis. No other significant spectral changes were observed. In conclusion, (³¹P) MRS can separate mild from moderate disease and these 2 groups from cirrhosis. The ability to differentiate these populations of patients has therapeutic implications and (³¹P) MRS, in some situations, would not only complement a liver biopsy but could replace it and be of particular value in assessing disease progression.

PMID: 12668971 [PubMed - indexed for MEDLINE]

28: Hepatology 2003 Apr;37(4):802-9

Hepatitis C virus infection in the general population: a community-based study in West Bengal, India.

Chowdhury A, Santra A, Chaudhuri S, Dhali GK, Chaudhuri S, Maity SG, Naik TN, Bhattacharya SK, Mazumder DN.

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Limited information is available about the prevalence and genotype distribution of hepatitis C virus (HCV) in the general population of India. A community-based epidemiologic study was carried out in a district in West Bengal, India. By a 1:3 sampling method, 3,579 individuals were preselected from 10,737 inhabitants of 9 villages of the district, of whom 2,973 (83.1%) agreed to participate. Twenty-six subjects (0.87%) were HCV antibody positive. The prevalence increased from 0.31%

in subjects <10 years of age to 1.85% in those ≥60 years. No difference in prevalence between men and women was observed. Serum alanine aminotransferase (ALT) levels were elevated in 30.8% (8 of 26) of anti-HCV-positive subjects compared with 3.2% (94 of 2,947) anti-HCV-negative subjects (P <.001). HCV RNA was detectable in 80.8% (95% CI, 65.6%-95.91%) of the anti-HCV-positive subjects by reverse transcription-primed polymerase chain reaction (RT-PCR). The participants were HCV types 1b in 2 (9.5%), 3a in 8 (38.1%), 3b in 6 (28.6%), and unclassified in 5 (23.8%). Nucleotide sequencing and phylogenetic analysis assigned the unclassified type to genotype 3e. In conclusion, this study provides general population-based estimates of HCV prevalence, including genotypes, from a South Asian country. Although the prevalence of HCV infection in this population was lower than that reported from industrialized countries of the west, the total reservoir of infection is significant and calls for public health measures, including health education to limit the magnitude of the problem. PMID: 12668973 [PubMed - indexed for MEDLINE]

29: Hepatology 2003 Apr;37(4):795-801

Racial differences in the relationship between hepatitis C infection and iron stores.

Ioannou GN, Dominitz JA, Weiss NS, Heagerty PJ, Kowdley KV.

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Black race and increased hepatic iron stores predict poor response to interferon treatment for chronic hepatitis C virus (HCV) infection. We tested the hypothesis that these 2 observations are linked by investigating whether HCV-infected African-Americans have increased iron stores relative to uninfected persons. Using data from the third National Health and Nutrition Examination Survey (NHANES III), we determined the risk of having increased iron stores, defined as elevation of both serum ferritin and transferrin-iron saturation (TS), in HCV-RNA-positive blacks (n = 100) and nonblacks (n = 126) relative to HCV-RNA-negative blacks (n = 4,002) and nonblacks (n = 10,943). HCV-positive blacks were 5.4 times (95% CI, 1.2 to 24) more likely to have increased iron stores than HCV-positive nonblacks. The proportion of HCV-positive blacks who had increased iron stores was 16.4% among those with abnormal liver enzymes and 2.8% among those with normal liver enzymes, compared with only 0.6% among HCV-negative blacks. After adjustment for age, alcohol intake, gender, menopausal status, education, body mass index, and poverty index, HCV-positive blacks with abnormal liver enzymes had an elevated risk of having increased iron stores (odds ratio, 17.8; 95% CI, 5.1 to 63). In contrast, among persons of other races, there was a much smaller difference in the proportion of persons with increased iron stores between HCV-positive persons with (3.4%) or without (1.4%) abnormal liver enzymes and HCV-negative persons (0.9%). In conclusion, a greater proportion of blacks than persons of other races respond to HCV infection with an increase in iron stores. This finding may partly explain the reduced response of HCV-positive African-Americans to antiviral treatment.

PMID: 12668972 [PubMed - indexed for MEDLINE]

30: Hepatology 2003 Mar;37(3):520-7

Comment in:

Hepatology. 2003 Mar;37(3):507-9.

Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis.

Velazquez RF, Rodriguez M, Navascues CA, Linares A, Perez R, Sotorrios NG, Martinez I, Rodrigo L.

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Department of Gastroenterology, Hospital de Cabuenes, Gijon, Spain.

Better knowledge of the risk factors associated with the appearance of hepatocellular carcinoma (HCC) could improve the efficacy of surveillance programs. A total of 463 patients aged 40 to 65 years with liver cirrhosis in Child-Pugh class A or B were included in a program of early diagnosis. The predictive value of different risk factors was evaluated using the Kaplan-Meier method and Cox regression model. Thirty-eight patients developed HCC. In the multivariate analysis, 4 variables showed an independent predictive value for the development of HCC: age 55 years or older, antibody to hepatitis C virus (anti-HCV) positivity, prothrombin activity 75% or less, and platelet count less than $75 \times 10^3/\text{mm}^3$. According to the contribution of each of these factors to the final model, a score ranging between 0 and 4.71 points was constructed to

allow the division of patients into 2 different risk groups. The low-risk group included those with a score of 2.33 points or less ($n = 270$; 4 with HCC; cumulative incidence of HCC at 4 years, 2.3%), and the high-risk group included those with a score greater than 2.33 ($n = 193$; 34 with HCC; cumulative incidence of HCC at 4 years, 30.1%) ($P = .0001$). In conclusion, a simple score made up of 4 clinical and biological variables allowed us to distinguish 2 groups of cirrhotic patients at high and low risk for the development of HCC. We believe this score can be useful in establishing a subset of cirrhotic patients in whom a surveillance program for early detection of HCC could be unjustified.

PMID: 12601348 [PubMed - indexed for MEDLINE]

31: Hepatology 2003 Mar;37(3):568-76

Ribavirin and interferon is effective for hepatitis C virus clearance in hepatitis B and C dually infected patients.

Liu CJ, Chen PJ, Lai MY, Kao JH, Jeng YM, Chen DS.

Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.

Ribavirin and interferon (IFN) are an effective treatment in 30% to 60% of patients with chronic hepatitis C. Whether they are also effective in dually infected patients with hepatitis B and C is unknown. Twenty-four patients with chronic hepatitis seropositive for both hepatitis B surface antigen and antibody to HCV received ribavirin 1,200 mg daily for 6 months, together with 6 million units (MU) IFN-alpha 2a thrice weekly for 12 weeks and then 3 MU for another 12 weeks. Serum HCV RNA was positive in 21 patients (group I, serum HBV DNA positive in 17 patients) and negative in 3 patients (group II, all HBV DNA positive) by Amplicor (Cobas Amplicor Monitor, Roche Diagnostics, Branchburg, NJ). Serum alanine aminotransferase (ALT), HCV RNA, and hepatitis B virus (HBV) DNA were monitored regularly for 12 months. Another 30 patients with chronic hepatitis C alone receiving the same regimen, served as controls. The serum HCV clearance rate in group I patients (43%) was comparable with that in controls (60%, $P = .63$) 24 weeks posttreatment. The serum ALT normalization rate in group I and group II patients was 43% and 0%, respectively, 24 weeks posttreatment. After treatment, resurgence of HBV and HCV was encountered in 4 group I patients and 1 group II patient, respectively. In conclusion, in hepatitis B and C dually infected patients, combination of IFN with ribavirin can achieve a sustained HCV clearance rate comparable with hepatitis C alone. In dually infected patients, the treatment may alter the dominant, ruling hepatitis virus.

PMID: 12601355 [PubMed - indexed for MEDLINE]

32: Hepatology 2003 Mar;37(3):507-9

Comment on:

Hepatology. 2003 Mar;37(3):520-7.

HCC surveillance: who is the target population?

Bruix J, Llovet JM.

Publication Types:

Comment

Editorial

PMID: 12601346 [PubMed - indexed for MEDLINE]

33: Hepatology 2003 Mar;37(3):577-89

Erratum in:

Hepatology. 2003 Apr;37(4):956.

Novel CD4+ and CD8+ T-cell determinants within the NS3 protein in subjects with spontaneously resolved HCV infection.

Wertheimer AM, Miner C, Lewinsohn DM, Sasaki AW, Kaufman E, Rosen HR.

Department of Medicine and Research Services, Portland Veterans Affairs Medical Center/Oregon Health and Science University, Portland, OR 97207, USA.

Spontaneous resolution of hepatitis C virus (HCV) infection is a relatively infrequent event, and these individuals provide a unique opportunity to characterize correlates of protective immunity as an important first step in the development of vaccine candidates. The aim of this study was to directly and comprehensively enumerate HCV-nonstructural protein 3 (NS3) specific CD4(+) and CD8(+) T cells ex vivo from HLA diverse individuals who had been successful in spontaneously resolving HCV infection. We measured interferon gamma (IFN-gamma) production with an ELISPOT assay using magnetic bead-separated CD4(+) or CD8(+) T cells in response to autologous DCs that had been pulsed with 15mer per peptides overlapping by 11 amino acids and spanning all of the NS3 protein (150 total peptides). All subjects with spontaneously recovered HCV infection demonstrated vigorous and multispecific CD4(+) T-cell responses to NS3 peptides, and 6 of 10 subjects demonstrated CD8(+) T-cell responses. More importantly, we identified novel, previously unpredicted antigenic regions, which in most cases elicited high frequencies within a given individual. In conclusion, subjects who have spontaneously eradicated HCV infection up to 35 years earlier demonstrate persistent CD4(+) and CD8(+) T-cell responses specific to NS3. By providing a comprehensive screening of all potential T-cell epitopes contained in the NS3 region, our strategy defines the breadth of the T-cell response and identifies novel, unpredicted specificities.

PMID: 12601356 [PubMed - indexed for MEDLINE]

34: Hepatology 2003 Mar;37(3):493-503

Genetic polymorphisms and the progression of liver fibrosis: a critical appraisal.

Battaller R, North KE, Brenner DA.

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Liver fibrosis is a highly dynamic process in which multiple genes interact with environmental factors. Recent human epidemiologic studies have identified possible polymorphisms in a number of candidate genes that influence the progression of liver fibrosis. These genetic factors could explain the broad spectrum of responses to the same etiologic agent found in patients with chronic liver diseases. Polymorphisms in genes encoding immunoregulatory proteins, proinflammatory cytokines, and fibrogenic factors may influence disease progression in patients with alcohol-induced liver disease, primary biliary cirrhosis, or chronic hepatitis C. However, some of the studies have yielded contradictory results. For example, conflicting results have been obtained in studies assessing the role of mutations in the hemochromatosis gene on fibrosis progression in patients with chronic hepatitis C. Large-scale, well-designed studies are required to clarify the actual role of this factor and other genetic variants in liver fibrosis.

Publication Types:

Review

Review, Tutorial
PMID: 12601343 [PubMed - indexed for MEDLINE]

35: Int J Cancer 2003 Apr 10;104(3):310-7

CYP enzyme polymorphisms and susceptibility to HCV-related chronic liver disease and liver cancer.

Silvestri L, Sonzogni L, De Silvestri A, Gritti C, Foti L, Zavaglia C, Leverì M, Cividini A, Mondelli MU, Civardi E, Silini EM.

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Cancer risk can be influenced by the exposure to endogenous or environmental toxins. Polymorphic enzymes involved in the metabolic activation/detoxification of carcinogens may account for individual variations of risk. We studied the polymorphisms of five enzymes of the P450 superfamily, CYP1A1, CYP1A2, CYP2D6, CYP2E1 and CYP3A4, as risk factors for liver disease progression and cancer in hepatitis C virus-infected patients. CYP genotyping was performed by polymerase chain reaction (PCR) restriction fragment length polymorphism or allele-specific PCR. Different stages of disease were considered, as follows: 90 asymptomatic carriers and 87 chronic hepatitis, 92 cirrhosis and 91 hepatocellular carcinoma (HCC) cases. Reference allele frequencies were obtained from 99 blood donors. Allele distributions among categories were compared using the chi(2) test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to express relative risks. Independent associations were modeled by correspondence analysis and logistic regression. Frequencies of the CYP1A1 highly inducible alleles, MspI m2 and Val, were increased in liver disease patients compared with carriers; no specific association with HCC was found. The high-activity CYP2E1 c2 allele was underrepresented among HCC patients with respect to other HCV categories, including cirrhosis. CYP2D6 poor metabolizer (PM) genotypes were significantly more frequent in healthy subjects (7.1%) and carriers (11.1%) than in hepatitis/cirrhosis (4.6%) and HCC (1.2%) patients. This was confirmed by multivariable analysis. PM genotypes protected against progressive disease as ORs reduced proportionally to stage. The age at diagnosis for HCC was anticipated in non-PM individuals. No differences were seen for CYP1A2 and CYP3A4 genes. Polymorphic variants of CYP genes may contribute to the progression of liver disease and HCC risk in HCV-infected subjects. Copyright 2003 Wiley-Liss, Inc.

PMID: 12569554 [PubMed - indexed for MEDLINE]

36: Ir Med J 2003 Mar;96(3):73-7

An investigation of the psychosocial impact of a Compensation Tribunal on women with iatrogenic hepatitis C infection.

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The aim of this study was to investigate the psychosocial impact of a Compensation Tribunal in women with an iatrogenic hepatitis C virus (HCV) infection. Eighty-three women diagnosed with an iatrogenic HCV infection were recruited, 19 women were Pre-Tribunal and 64 women were post-Tribunal. Both standardised and disease specific psychological measures were used. A series of t-tests revealed no differences in psychological well-being and adjustment to HCV infection in women pre and post Compensation Tribunal. Chi-square tests revealed no association between PCR status and 1) psychological well-being and 2) experience of anger/blame in women post-Compensation Tribunal. A further series of t-tests revealed that women with high levels of anger and blame post-Compensation Tribunal perceived their future as more uncertain, experienced more pain, low self-esteem and psychological distress, viewed their ability to work as impeded and complained of increased stress preparing for their Compensation Tribunal. This study suggests that poor adjustment in women with an iatrogenic HCV infection post-Compensation Tribunal is not associated with

attendance at a Compensation Tribunal nor PCR status but rather to experiences of anger and blame.

PMID: 12722782 [PubMed - indexed for MEDLINE]

37: J Acquir Immune Defic Syndr 2003 Apr 1;32(4):465-6

Is treatment failure for hepatitis C virus infection in HIV-positive drug users associated with a shift in HCV genotypes?

Soriano V, Perez-Olmeda M, Rios P, Nunez M, Garcia-Samaniego J, Gonzalez-Lahoz J.

Publication Types:

Letter

PMID: 12640209 [PubMed - indexed for MEDLINE]

38: J Acquir Immune Defic Syndr 2003 Mar 1;32(3):348-9

Hepatitis C virus in patients with HIV infection and lipodystrophy.

Rodriguez-Guardado A, Maradona JA, Asensi V, Carton JA, Casado L.

Publication Types:

Letter

PMID: 12626899 [PubMed - indexed for MEDLINE]

39: J Acquir Immune Defic Syndr 2003 Mar 1;32(3):259-67

Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome.

Puoti M, Torti C, Ripamonti D, Castelli F, Zaltron S, Zanini B, Spinetti A, Putzolu V, Casari S, Tomasoni L, Quiros-Roldan E, Favret M, Berchich L, Grigolato P, Callea F, Carosi G; HIV-HCV Co-Infection Study Group.

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OBJECTIVES: To assess incidence, risk factors, histology, and outcome of severe hepatotoxicity (SH) during antiretroviral treatment (ART). **METHODS:** Seven hundred fifty-five HIV-seropositive patients consecutively prescribed new ART were selected. Liver function tests were assessed at baseline, after 1 month, and every 4 months thereafter. Liver biopsy was recommended in case of SH (i.e., increase in liver enzymes ≥ 10 times the upper limit of normal or 5 times baseline if markedly abnormal). **RESULTS:** Twenty-six cases of SH were observed with an incidence of 4.2% person-years. Liver failure (LF) was rarely seen (1.1 per 100 person-years). Liver damage was invariably observed in patients with chronic viral hepatitis. Liver histology showed exacerbation of viral hepatitis in all 16 patients for whom a liver biopsy was available at the time of SH. A direct correlation was found between alanine aminotransferase increase and increase in CD4 T-cell count in patients with SH ($r = 0.53$, $p < .001$). Death occurred during follow-up in 7 of 26 (27%) patients, all of whom showed LF and baseline CD4+ count less than 200 cells/mm³ (7/7 patients = 100% vs. 8/19 patients without LF; $p < .01$). Relapse of SH was observed after ART was recommenced in 7 of 17 (41%) patients. Five of these 7 patients did not show further SH relapse after treatment with interferon. **CONCLUSIONS:** This study provides estimates of SH and LF in a large population-based setting where hepatitis C virus coinfection is highly prevalent and provides indications that liver damage may be caused by immune reconstitution and related exacerbation of viral hepatitis. A strict follow-up for hepatotoxicity is mandatory when ART is initiated in patients with < 200 CD4+ T cells/mm³. Antihepatitis pre- or comedication could be an effective preventive or curative measure.

Publication Types:

Clinical Trial

PMID: 12626885 [PubMed - indexed for MEDLINE]

40: J Clin Microbiol 2003 Mar;41(3):1091-100

Hepatitis C virus subtyping by a core-envelope 1-based reverse transcriptase PCR assay with sequencing and its use in determining subtype distribution among Danish patients.

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A reverse transcriptase PCR (RT-PCR) assay using conserved primers deduced from the core-envelope 1 (C-E1) region of the hepatitis C virus (HCV) genome was developed for subtyping purposes. The sensitivity and specificity of this assay tested against two HCV reference panels containing genotype 1 through 5 subtypes were similar to those of an RT-PCR assay from the 5'-untranslated region (5'-UTR). The sensitivity of the RT-PCR typing assay in the more variable C-E1 region was, however, lower than that of the RT-PCR in the highly conserved 5'-UTR when testing multiple clinical samples. Thus, 71 (88%) of 81 consecutive samples from hospitalized Danish patients positive for HCV antibodies and RNA (5'-UTR) were positive also in the C-E1 RT-PCR assay. Phylogenetic analysis of the E1 sequences obtained by direct sequencing of HCV from two reference panels and 71 Danish patients allowed us to readily distinguish the subtypes. In contrast, phylogenetic analysis of their corresponding 5'-UTR sequences was able to predict only major genotypes. Three different genotypes and four subtypes were identified among Danish samples: 1a (43%), 1b (11%), 2b (6%), and 3a (39%). An isolate from a Somalian refugee was identified as a new HCV type related to Somalian isolates described as subtype 3h. The most common genotype in Denmark is genotype 1 (53%), which is the most difficult to treat. However, Denmark had the highest prevalence in Europe of subtype 3a, which responds more favorably to treatment. The described C-E1 RT-PCR with sequencing is suggested as an easy routine assay for definitive genotyping and subtyping of HCV.

PMID: 12624035 [PubMed - indexed for MEDLINE]

41: J Exp Med 2003 Mar 3;197(5):633-42

Infectious hepatitis C virus pseudo-particles containing functional E1-E2 envelope protein complexes.

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The study of hepatitis C virus (HCV), a major cause of chronic liver disease, has been hampered by the lack of a cell culture system supporting its replication. Here, we have successfully generated infectious pseudo-particles that were assembled by displaying unmodified and functional HCV glycoproteins onto retroviral and lentiviral core particles. The presence of a green fluorescent protein marker gene packaged within these HCV pseudo-particles allowed reliable and fast determination of infectivity mediated by the HCV glycoproteins. Primary hepatocytes as well as hepato-carcinoma cells were found to be the major targets of infection in vitro. High infectivity of the pseudo-particles required both E1 and E2 HCV glycoproteins, and was neutralized by sera from HCV-infected patients and by some anti-E2 monoclonal antibodies. In addition, these pseudo-particles allowed investigation of the role of putative HCV receptors. Although our results tend to confirm their involvement, they provide evidence that neither LDLr nor CD81 is sufficient to mediate HCV cell entry. Altogether, these studies indicate that these pseudo-particles may mimic the early infection steps of parental HCV and will be suitable for the development of much needed new antiviral therapies.

PMID: 12615904 [PubMed - indexed for MEDLINE]

42: J Gen Virol 2003 Mar;84(Pt 3):545-54

Characterization of secreted and intracellular forms of a truncated hepatitis C virus E2 protein expressed by a recombinant herpes simplex virus.

Lucas M, Tsitoura E, Montoya M, Laliotou B, Aslanoglou E, Kouvatsis V, Entwisle C, Miller J, Klennerman P, Hadziyannis A, Hadziyannis S, Borrow P, Mavromara P. Molecular Virology Laboratory, Hellenic Pasteur Institute, 127 Vas. Sofias Ave, Athens 115 21, Greece.

A replication-defective herpes simplex virus type 1 (HSV-1) recombinant lacking the glycoprotein H (gH)-encoding gene and expressing a truncated form of the hepatitis C (HCV) E2 glycoprotein (E2-661) was constructed and characterized. We show here that cells infected with the HSV/HCV recombinant virus efficiently express the HCV E2-661 protein. Most importantly, cellular and secreted E2-661 protein were both readily detected by the E2-conformational mAb H53 and despite the high expression levels, only limited amounts of misfolded aggregates were detected in either the cellular or secreted fractions. Furthermore, cell-associated and secreted E2-661 protein bound to the major extracellular loop (MEL) of CD81 in a concentration-dependent manner and both were highly reactive with sera from HCV-infected patients. Finally, BALB/c mice immunized intraperitoneally with the recombinant HSV/HCV virus induced high levels of anti-E2 antibodies. Analysis of the induced immunoglobulin G (IgG) isotypes showed high levels of IgG2a while the levels of the IgG1 isotype were significantly lower, suggesting a Th1-type of response. We conclude that the HSV-1 recombinant virus represents a promising tool for production of non-aggregated, immunologically active forms of the E2-661 protein and might have potential applications in vaccine development.

PMID: 12604804 [PubMed - indexed for MEDLINE]

43: J Infect Dis 2003 Apr 1;187(7):1071-4

Interferon and ribavirin therapy for chronic hepatitis C virus genotype 6: a comparison with genotype 1.

Hui CK, Yuen MF, Sablon E, Chan AO, Wong BC, Lai CL.

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Because there is a lack of data on the treatment outcome of patients who carry hepatitis C virus (HCV) genotype 6, we conducted a prospective study, to compare the effect of interferon and ribavirin therapy in HCV genotypes 1 and 6, of patients with seropositive anti-HCV, persistently elevated alanine transaminase levels, and detectable HCV RNA. Patients were treated with subcutaneous recombinant interferon alpha-2b and ribavirin for 12 months. Of 40 patients, 16 had genotype 6, and 24 had genotype 1. An end-of-treatment response was detected in 12 (75%) patients with genotype 6 and in 10 (41.6%) patients with genotype 1 ($P=.05$). A sustained virological response (SVR) was present in 10 (62.5%) patients with genotype 6 and in 7 (29.2%) patients with genotype 1 ($P=.04$). Genotype 6 has a better response than genotype 1 and is associated with a higher SVR.

Publication Types:

Clinical Trial

PMID: 12660921 [PubMed - indexed for MEDLINE]

44: J Infect Dis 2003 Mar 15;187(6):982-7

Mutations within the CD81-binding sites and hypervariable region 2 of the envelope 2 protein: correlation with treatment response in hepatitis C virus-infected patients.

Hofmann WP, Sarrazin C, Kronenberger B, Schonberger B, Bruch K, Zeuzem S. Innere Medizin II, Medizinische Klinik und Poliklinik, Universitat des Saarlandes, Homburg, Germany.

The hepatitis C virus (HCV) envelope 2 (E2) protein interacts with the cellular receptor CD81 in vitro. Within E2, 2 CD81-binding sites were described. E2-CD81

interaction has been shown to modulate B and T cell function. The clinical importance of mutations within the CD81-binding sites and overlapping hypervariable region 2 (HVR2) in correlation with response to antiviral treatment is unknown. Fifty-five patients infected with HCV-1b or HCV-3a underwent interferon-alpha-based treatment. The E2 gene, comprising the CD81-binding sites and HVR2, was sequenced from pretreatment serum samples. The number of mutations within CD81-binding sites was not correlated with virologic treatment response in HCV-1b- and HCV-3a-infected patients. Within HVR2, the total number of mutations was significantly higher in HCV-1b-infected patients with a sustained response to interferon-alpha-based treatment (3.9; range, 1-6) than in those with relapse (2.9; range, 1-5) or those who did not respond (2.8; range, 1-5) ($P = .041$). However, when the same analyses were based only on functionally nonconserved mutations, no significant differences were observed.

Publication Types:

Clinical Trial

PMID: 12660945 [PubMed - indexed for MEDLINE]

45: J Infect Dis 2003 Mar 1;187(5):872; author reply 872-4

Comment on:

J Infect Dis. 2002 Mar 1;185(5):567-72.

Perinatal hepatitis C virus transmission--role of human immunodeficiency virus infection and injection drug use.

Armstrong GL, Perz JF, Alter MJ.

Publication Types:

Comment

Letter

PMID: 12599064 [PubMed - indexed for MEDLINE]

46: J Med Virol 2003 Apr;69(4):538-45

Virus-inhibiting surgical glove to reduce the risk of infection by enveloped viruses.

Bricout F, Moraillon A, Sonntag P, Hoerner P, Blackwelder W, Plotkin S.

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Needle puncture and other accidents that occur during surgery and other procedures may lead to viral infections of medical personnel, notably by hepatitis C (HCV) and human immunodeficiency virus (HIV), now that hepatitis B can be prevented by vaccination. A new surgical glove called G-VIR, which contains a disinfecting agent for enveloped viruses, has been developed. Herpes simplex type 1 (HSV) was used as a standard enveloped virus in both in vitro and in vivo tests of the virucidal capacity of the glove. Bovine viral diarrhea virus (BVDV) and feline immunodeficiency virus (FIV) were used as models for HCV and HIV, respectively. For in vitro study, a contaminated needle was passed through a glove and residual virus was titrated; for in vivo studies, animals were stuck with a contaminated needle through a glove. Despite variation in virus enumeration inherent in the puncture technique, statistical evaluation showed that infection was reproducibly and substantially reduced by passage through the virucidal layer. For BVDV, the amount of virus passing through the virucidal glove was reduced in 82% of pairwise comparisons with control gloves that lacked the virucidal agent; when plaque counts were adjusted to a common dilution, the median count for the virucidal glove was on the average reduced >10-fold. In experiments in which the proportion of wells infected with FIV was measured, the ratio of TCID₅₀ values (control glove to G-VIR) was >15, and probably much higher. For HSV, the amount of virus passing through the virucidal glove was reduced in 81% of comparisons with control gloves; the median of adjusted plaque counts was reduced on the average approximately eightfold or ninefold. In vivo tests with FIV and HSV in cats and mice, respectively,

found smaller percentage reductions in infection than the in vitro tests but confirmed the virucidal effect of the gloves. Copyright 2003 Wiley-Liss, Inc.
PMID: 12601762 [PubMed - indexed for MEDLINE]

47: J Med Virol 2003 Apr;69(4):489-94

Unexpected distribution of hepatitis C virus genotypes in patients on hemodialysis and kidney transplant recipients.

Perez RM, Ferraz ML, Figueiredo MS, Contado D, Koide S, Ferreira AP, Cendoroglo Neto M, Medina Pestana JO, Silva AE.

Division of Gastroenterology, Universidade Federal de Sao Paulo, Brazil.

The distribution of hepatitis C virus (HCV) genotypes in patients on hemodialysis and in kidney transplant recipients was compared with that observed in a control group composed of HCV-infected individuals from the general population. A total of 340 patients were included in the study: 46 with end-stage renal disease on regular hemodialysis treatment, 22 kidney transplant recipients and 272 controls matched for sex and age at a 4:1 ratio (controls to patient). HCV genotype was determined by sequencing of the 5' untranslated region of the HCV genome. No difference was observed in the distribution of HCV genotypes in hemodialysis patients and renal transplant patients ($P = 0.47$). However, when each of these groups was compared with the control group, a significant difference was detected in the genotype distribution ($P < 0.001$). In

hemodialysis and renal transplant patients the most prevalent subtype was 1a, followed by 1b, 3, and other less prevalent genotypes (2, 4, and 5), whereas in the control group the most prevalent subtype was 1b, followed by 3, 1a, and others.

That observation may reflect differences in the epidemiology of HCV infection, viral characteristics and host factors in renal patients in comparison to the control group.

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PMID: 12601756 [PubMed - indexed for MEDLINE]

48: J Med Virol 2003 Apr;69(4):475-81

Sequencing of human-viral DNA junctions in hepatocellular carcinoma from patients with HCV and occult HBV infection.

Tamori A, Nishiguchi S, Kubo S, Enomoto M, Koh N, Takeda T, Shiomi S, Hirohashi K, Kinoshita H, Otani S.

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DNA of free hepatitis B viruses (HBV) has been detected in the liver of patients infected with hepatitis C virus (HCV). It is unknown whether HBV DNA is integrated into such livers; if so, it may affect hepatocarcinogenesis. Hepatocellular carcinomas (HCCs) from 34 patients without HBV surface antigen (HBsAg) and with anti-HCV, and from 7 patients with HBsAg and without anti-HCV as controls, were examined, using the cassette-ligation-mediated polymerase chain reaction and primers based on HBV DNA sequence. In the controls, HBV DNA had been integrated into human DNA of all HCCs. On the basis of HBV DNA in tumor tissue, 23 of the 34 patients with anti-HCV had occult infection. Junctions between human DNA and HBV DNA were detected in 10 of the 34 patients without HBsAg and with anti-HCV. HBV DNA was integrated into chromosome 11q in 4 of the 10 HCCs with junctions. The DNA to either side of the human-viral junctions was sequenced. Clinically, the mean tumor size of these 10 HCCs was 39 mm; that of the 24 HCCs without integrated HBV was 25 mm. The surrounding tissue was cirrhotic in 2 of the 10 former HCCs and in 16 of the latter 24 HCCs. In conclusion, integrated HBV was detected in some patients with HCV infection; in these patients, the integrated DNA was associated with accelerated hepatocarcinogenesis. Copyright 2003 Wiley-Liss, Inc.

PMID: 12601754 [PubMed - indexed for MEDLINE]

49: J Med Virol 2003 Apr;69(4):482-8

Evolution of hepatitis C virus quasiespecies in renal transplant patients with de novo glomerulonephritis.

Kamar N, Rostaing L, Boulestin A, Sandres K, Dubois M, Ribes D, Modesto A, Durand D, Izopet J.

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Long-term renal allograft survival in kidney transplant recipients infected by hepatitis C virus (HCV) may be influenced by the occurrence of de novo glomerulopathy associated with this virus. Therefore, we studied the evolution of HCV quasiespecies in kidney transplant recipients infected by HCV with or without de novo

glomerulopathy. The hypervariable region 1 (HVR-1) of the virus envelope was analyzed by cloning and sequencing 20 clones per sample to assess complexity and diversity from six kidney transplant patients who developed de novo glomerulopathy (group I) matched to six kidney transplant recipients without glomerular disease (group II), according to age, time since renal transplantation, and HCV genotype.

Two sera were analyzed for each patient: one at the time of renal transplantation and the other at the time of appearance of de novo glomerulopathy, or after a similar duration since transplantation in group II. Overall, there was a significant increase of HCV viremia after the transplantation. This increase did not differ significantly between group I (+0.5 log copies/ml) and group II patients (+1 log copies/ml). The intersample diversity of HCV was similar in the two groups.

Complexity and viral diversity were also similar at the time of transplantation. By contrast, complexity, diversity, and the proportion of nonsynonymous substitutions per nonsynonymous site were significantly higher after transplantation in group I patients. Our findings suggest a higher immune response and/or a particular cytokine production in patients developing de novo glomerulopathy rather than a direct effect of HCV on renal cells. Copyright 2003 Wiley-Liss, Inc.

PMID: 12601755 [PubMed - indexed for MEDLINE]

50: J Med Virol 2003 Mar;69(3):357-66

Processing of hepatitis C virus core protein is regulated by its C-terminal sequence.

Kato T, Miyamoto M, Furusaka A, Date T, Yasui K, Kato J, Matsushima S, Komatsu T, Wakita T.

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Polyprotein processing of plus-strand RNA viruses is important in the regulation of gene production and replication. The core protein of hepatitis C virus (HCV), constructing the viral particle, is processed from its precursor polyprotein and observed as two forms, p23 and p21. Production of p21 by cleavage at the C-terminus of p23 is considered crucial to viral assembly and replication. In this study, this processing step was compared between clones isolated from two patients with fulminant hepatitis and from five patients with chronic hepatitis by an in vitro translation assay and cell transfection assay. The p21 core protein was predominant from the clone isolated from one of the fulminant hepatitis patient (p21 core protein production was 65.98%), while p23 was abundant with clones from five chronic hepatitis patients (p21 core protein production was 7.11+/-1.62%) and clone from another fulminant hepatitis patient (p21 core protein production was 13.36%). Investigations with chimeric and mutation-introduced constructs revealed that four amino acid residues in the C-terminus of the core region are responsible for this difference. The data suggest that core protein processing is regulated by C-terminus mutations.

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PMID: 12526046 [PubMed - indexed for MEDLINE]

51: J Med Virol 2003 Mar;69(3):350-6

Changes in hypervariable region 1 of the envelope 2 glycoprotein of hepatitis C virus in children and adults with humoral immune defects.

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The N-terminal end of the hepatitis C virus (HCV) envelope glycoprotein E2 contains a stretch of 27 amino acids that exhibit increased variability. This hypervariable region 1 (HVR-1), as it is normally referred to, is thought to contain epitopes that come under humoral immune attack. In the present study, 10 patients (5 children and 5 adults) with humoral immune defects and chronic HCV infection were investigated, to see how HVR-1 sequences behave over time in these patients who are unable to produce antibodies. Amplicons of this region showed little or no variation at all over time, indicating that quasispecies variation in this region is driven by the host's humoral immune response. Copyright 2003 Wiley-Liss, Inc. PMID: 12526045 [PubMed - indexed for MEDLINE]

52: J Med Virol 2003 Mar;69(3):344-9

Intermittent detection of hepatitis C virus (HCV) in semen from men with human immunodeficiency virus type 1 (HIV-1) and HCV.

Pasquier C, Bujan L, Daudin M, Righi L, Berges L, Thauvin L, Berrebi A, Massip P, Puel J, Izopet J.

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HCV is usually transmitted via the blood, but HCV RNA has been detected recently in seminal fluid. This study was done to study HCV seminal shedding and factors that could influence the presence of HCV in the seminal fluid of men coinfectd with HCV and HIV-1. HCV and HIV-1 genomes were assayed in multiple paired blood and semen samples obtained from 35 men enrolled in an assisted medical procreation protocol. HCV RNA was found intermittently in semen samples from 9 patients (25.7%). Samples from 9 men with HCV RNA in their semen and 26 men without were compared to further analyze these parameters. No correlation was found between HCV RNA in the seminal fluid and age, HCV virus load, the duration of HIV-1 infection, HIV treatment, the CD4(+) cell count, HIV-1 virus load or HIV-1 detection in the semen. The intermittent detection of HCV RNA in semen samples support the systematic search for HCV RNA in semen and the use of processed spermatozoa in assisted medical procreation of infertile HCV serodiscordant couples. Copyright 2003 Wiley-Liss, Inc. PMID: 12526044 [PubMed - indexed for MEDLINE]

53: J Med Virol 2003 Mar;69(3):339-43

Prevalence and clinical significance of circulating cryoglobulins in HIV-positive patients with and without co-infection with hepatitis C virus.

Fabris P, Tositti G, Giordani MT, Romano L, Betterle C, Pignattari E, Tagliaferri C, Muratori P, Manfrin V, de Lalla F.

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Although hepatitis C virus (HCV) is a recognized cause of circulating cryoglobulins, the role of human immunodeficiency virus (HIV) in the pathogenesis of cryoglobulinemia has not been investigated extensively. To evaluate the prevalence of circulating cryoglobulins and to assess the relationship with clinical and virological parameters, 162 HIV-positive subjects (84 anti-HCV(+)) were tested for cryoglobulins, C3, C4, RF, autoantibodies, HIV-viral titer, and CD4(+) count. Anti-HCV-positive subjects were tested for HCV-RNA, HCV-viral titer, and HCV genotype. All patients were examined for the presence of signs or symptoms of vasculitis and

tested for cryoglobulins using a standard biochemical assay. Cryoglobulins were found in 30 (18.5%) cases. Of the 30 positive cases, 29 (96.7%) were anti-HCV-positive and 28 (93.3%) HCV-RNA-positive. The presence of cryoglobulins was significantly associated ($P < 0.01$) with HCV-RNA positivity (OR = 27), liver cirrhosis (OR = 16), decreased levels of C3 (OR = 8.6), C4 (OR = 13.6), increased levels of IgG and IgM (OR = 6.1 and 7.9, respectively), and RF positivity (OR = 6.3), but was unrelated to CD4(+) cell count, HIV viral load, diagnosis of AIDS, HCV viral load and the presence of autoantibodies. Interestingly, the presence of cryoglobulins was not significantly associated with signs and symptoms commonly associated with cryoglobulinemia. In conclusion, HIV infection does not seem to play a significant role in the production of circulating cryoglobulins, which strongly correlates with HCV co-infection and liver cirrhosis. Typical signs and symptoms of cryoglobulinemia do not correlate with the detection of circulating cryoglobulins in HIV and HCV patients. Copyright 2003 Wiley-Liss, Inc.

PMID: 12526043 [PubMed - indexed for MEDLINE]

54: J Med Virol 2003 Mar;69(3):331-8

An outbreak of HBV and HCV infection in a paediatric oncology ward: epidemiological investigations and prevention of further spread.

Dumpis U, Kovalova Z, Jansons J, Cupane L, Sominskaya I, Michailova M, Karayiannis P, Gardovska D, Viazov S, Ross S, Roggendorf M, Pumpens P. Biomedical Research and Study Centre, University of Latvia, Riga, Latvia. uga@biomed.lu.lv

Hospital-acquired hepatitis B (HBV) and C virus (HCV) infections continue to occur despite increased awareness of this problem among the medical community. One hundred six patients were infected in a haematology oncology ward for children, over the time period 1996 to 2000. Serum samples from 45 such patients and 3 from infected medical personnel were used for nucleic acid amplification. HBV core, as well as HCV core and hypervariable region 1 (HVR1) nucleotide sequences, were analysed by phylogenetic tree analysis, in order to characterize the epidemiological pattern of viral transmission on the ward. Samples from 32 patients were positive for HBV-DNA or HCV-RNA by PCR. Ten patients were positive for both markers. Seventeen out of twenty-three HCV core gene sequences were found to be evolutionarily related and clustered separately from other local sequences in the phylogenetic tree, indicating nosocomial transmission. This was confirmed by analysis of HVR1 gene sequences. One nurse and one physician from the ward were HCV RNA positive, but their HCV sequences were not related evolutionarily to those of the patient cluster. Fifteen out of nineteen HBV core gene sequences were also clustered together and were positioned separately in the relevant tree. Epidemiological investigation excluded a common source infection and indicated that spread of infection was most likely due to inappropriate infection control measures on the ward. No obvious risk factors for transmission were identified during the retrospective survey in patients with related sequences, except use of multidose vials for saline and poor staff compliance with routine hand hygiene procedures. The preventive measures that were introduced reduced the incidence of infection significantly. No new cases of HBV infection and only three anti-HCV seroconversions occurred over a period of 19 months. The introduction and maintenance of strict prevention measures over a 2 year period, combined with HBV vaccination, reduced significantly the incidence of new HCV and HBV infections. Copyright 2003 Wiley-Liss, Inc.

PMID: 12526042 [PubMed - indexed for MEDLINE]

55: J Med Virol 2003 Mar;69(3):313-23

Kinetics of HBV DNA and HBsAg in acute hepatitis B patients with and without coinfection by other hepatitis viruses.

Chulanov VP, Shipulin GA, Schaefer S, Gerlich WH.

Central Research Institute of Epidemiology, Russian Federal Aids Center Moscow, Russia.

The kinetics of hepatitis B virus (HBV) and its surface antigen (HBsAg) during acute hepatitis has not yet been studied accurately in a representative number of patients. The influence of coinfecting hepatitis viruses during the acute phase of infection is not known. Three to four serum samples from 21 patients with acute HBV monoinfection and 27 with coinfection were taken at intervals of 6-10 days and analyzed for the number of HBV genome equivalents (ge) by real time polymerase chain reaction (PCR) and for HBsAg quantity using Laurell electrophoresis. Log HBV ge/ml decreased during the follow-up from 6.8 +/- 1.1 to 5.1 +/- 1.0 to 4.2 +/- 0.8 to 3.3 +/- 1.1 (mean +/- SD). The half-life times of HBV ge increased from 1.6 days at the beginning to 4 days at the end. HbsAg decreased much slower: from 38 to 23 to 12 to 3.8 microg/ml. Half-life time was around 8 days at the beginning and 5.7 days at the end, but 11 patients showed a rapid elimination of HBsAg and HBV DNA. Hepatitis C virus (HCV) coinfection did not change the kinetics of HBV ge and HBsAg significantly. A moderate but significant suppression of HBV ge levels was observed in hepatitis D virus (HDV) coinfecting patients. HBsAg levels were, however, enhanced in this cohort. In conclusion, the data suggest that expression and elimination of HBV is in most patients with acute hepatitis B not altered by coinfecting hepatitis viruses. The initial decrease of HBV ge and HBsAg in serum appears to be caused by decay or non-specific removal in the absence of replacement. Copyright 2003

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PMID: 12526040 [PubMed - indexed for MEDLINE]

56: J Med Virol 2003 Mar;69(3):367-75

Hepatitis C virus molecular epidemiology in Uzbekistan.

Kurbanov F, Tanaka Y, Sugauchi F, Kato H, Ruzibakiev R, Zalyalieva M, Yunusova Z, Mizokami M.

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The aim of this study was to identify hepatitis C virus (HCV) genotypes and to estimate their prevalence in various risk groups and the regional distribution in Uzbekistan. Preliminary serological screening of 1,269 subjects revealed 6.5% anti-HCV-positive in a general population, 27.1% in patient groups, and 51.7% among intravenous drug users. HCV genotypes of 104 anti-HCV-positive subjects were determined using a PCR-genotyping system in core region, and the results were supported by nucleotide sequencing of the NS5B region. Genotype 1b identified in total 64.2%, was the most prevalent. The genotype 3a identified in 25.0% was the second one distributed. HCV genotypes 2a, 1a, 2b, and 3b were identified in 3.8%, 2.9%, 2.9%, and 1.0% of cases, respectively. The intravenous drug users were distinguished from other groups by having the highest prevalence of genotype 3a, i.e., 50.0%, higher than the 33.3% for genotype 1b in this group. Geographically, genotype 1b was common; genotype 3a was also found frequently in all three regions. Uncommon HCV genotypes (1a, 2a, 2b, and 3b) were found in comparatively greater variability in the western region. Molecular evolutionary analysis based on the NS5B region did not reveal specific clustering or indigenous strains among Uzbekistan HCV isolates. In summary, two main mechanisms of HCV infection distribution were observed in Uzbekistan: HCV 1b genotype infection is widespread through blood products, and HCV 3a genotype infection is spreading through the growing number of intravenous drug users. Copyright 2003 Wiley-Liss, Inc.

PMID: 12526047 [PubMed - indexed for MEDLINE]

57: J Med Virol 2003 Mar;69(3):376-83

Association of amino acid substitution pattern in nonstructural protein 5A of hepatitis C virus genotype 2a low viral load and response to interferon monotherapy.
Akuta N, Suzuki F, Tsubota A, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H.
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Patients with low titer (<0.5 mEq/ml) of hepatitis C virus (HCV) genotype 2a achieve high and sustained response (SR) rates to interferon (IFN) monotherapy, but we also encounter patients who are resistant to therapy. We explored the relationship between response to IFN and virological differences in such patients. We evaluated 159 consecutive naive patients with low titer of HCV genotype 2a who received IFN monotherapy. A case-control study matched for age, sex, and viral load was conducted to examine the substitution patterns in amino acid positions (amino acids) 2163-2254 of nonstructural (NS) 5A between nonresponders to ideal IFN dose (≥ 500 million units) (nonresponders; NR) and responder to less than ideal dose. Overall, 82.4% achieved SR. The substitution numbers in amino acids 2193-2254 were higher in SR than NR patients ($P < 0.05$). High proportions of patients with substitution at amino acid 2205 (mainly threonine [T] instead of alanine [A]), dual amino acids 2169 and 2205 (mainly A-T instead of T-A), and those without substitution at amino acids 2227 were NR ($P < 0.05$). Four of 7 NR patients achieved SR after receiving a second course of IFN. Their amino acids patterns at positions probably associated with sensitivity to IFN did not change at the start of initial and second therapies except for one patient, and they had lower viral load and were treated with higher IFN dose in the second course compared with the initial course. Our results suggest that substitution patterns in NS5A in patients with low titer of HCV genotype 2a may affect their response to IFN, but the response to therapy may be affected by mechanisms other than substitutions in this region. Copyright 2003 Wiley-Liss, Inc.

PMID: 12526048 [PubMed - indexed for MEDLINE]

58: J Med Virol 2003 Mar;69(3):384-90

Hepatitis C virus infection among pregnant women in Yaounde, Cameroon: prevalence, viremia, and genotypes.

Njouom R, Pasquier C, Ayouba A, Sandres-Saune K, Mfoupouendoun J, Mony Lobe M, Tene G, Thonnon J, Izopet J, Nerrienet E.

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Central Africa is considered to be an area of high endemic hepatitis C infection. To determine the prevalence of anti-HCV antibodies, HCV RNA, and the genotype distribution in Cameroon, 1,494 pregnant women attending antenatal care units in Yaounde, Cameroon were screened for HCV infection. Anti-HCV antibodies were detected with a 3rd generation ELISA (Monolisa anti-HCV plus version 2, BioRad, Richmond, CA). All anti-HCV antibody-positive sera were then tested with another 3rd generation ELISA (AxSYM) HCV version 3, Abbott Laboratories, Abbott Park, IL) and subsequently for HCV RNA (Amplicor HCV, Roche Diagnostics, Basel, Switzerland). Genotype was determined by phylogenetic analysis of the NS5b gene. Seventy-three pregnant women were found to be anti-HCV antibody positive by the first ELISA, but only 28 were anti-HCV positive by both ELISA. The prevalence of anti-HCV antibodies was thus 1.9% (28/1,494) (95% CI: 1.3-2.7%). 21/28 (75%) of the positive samples by both ELISA were HCV RNA positive. The 45 samples that were HCV antibody negative by the second ELISA were also HCV RNA negative. The HCV subtypes identified were 1a (24%), 2f (38%) and 4f (38%). In contrast to previous studies, anti-HCV antibodies were rare among pregnant women in Cameroon. The percentage of HCV seropositive pregnant women who had circulating HCV RNA was similar to that observed in Europe. Several HCV genotypes were found in Cameroon. Copyright 2003 Wiley-Liss, Inc.

PMID: 12526049 [PubMed - indexed for MEDLINE]

59: J Pediatr Hematol Oncol 2003 Mar;25(3):183

Comment on:

J Pediatr Hematol Oncol. 2003 Mar;25(3):184-92.

J Pediatr Hematol Oncol. 2003 Mar;25(3):209-14.

J Pediatr Hematol Oncol. 2003 Mar;25(3):215-22.

Comments from the editor-in-chief. Infectious complications of cancer treatment. Survivorship and treatment-related toxicities: how well are we doing?

Arceci RJ.

Publication Types:

Comment

Editorial

PMID: 12621234 [PubMed - indexed for MEDLINE]

60: J Public Health Med 2003 Mar;25(1):13-8

A survey of community pharmacists on prevention of HIV and hepatitis B and C: current practice and attitudes in Grampian.

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BACKGROUND: Prevention of infection with the blood-borne pathogens (BBPs) HIV and hepatitis B and C remains a major public health challenge. The aim of this study was to assess the activity, knowledge and attitudes of community pharmacists in Grampian in prevention of HIV and hepatitis B and C. METHOD: A questionnaire survey of community pharmacies was carried out in Grampian, a mixed urban-rural Health Board area in NE Scotland with a population of 532,432. RESULTS: Ninety-nine out of 128 (77 per cent) community pharmacies responded. Many pharmacies were providing services for drug misusers. Nearly all pharmacies stocked condoms, 57 pharmacists stated that they stocked extra-strong condoms, and two stocked dental dams. Two-thirds had leaflets relating to safer sex, HIV or hepatitis. Less than half stated that they had lists of local agencies dealing with drug-related or sexual health problems. Knowledge of the BBPs, and confidence in giving advice, were greater for HIV than for hepatitis B and C. Few were aware of recommendations for hepatitis B vaccination. The majority felt that in the future pharmacists could have a greater role in prevention of these infections. Principal barriers to preventive activity were described as time pressure, lack of a private area and lack of training. CONCLUSIONS: There is untapped potential for community pharmacists to be a focus for advice and information relating to prevention of HIV and hepatitis B and C; however, resources are needed to address the current barriers identified field.

PMID: 12669912 [PubMed - indexed for MEDLINE]

61: J Virol 2003 Apr;77(8):4781-93

Kinetics of CD4+ and CD8+ memory T-cell responses during hepatitis C virus rechallenge of previously recovered chimpanzees.

Nascimbeni M, Mizukoshi E, Bosmann M, Major ME, Mihalik K, Rice CM, Feinstone SM, Rehermann B.

Liver Diseases Section, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA. The immunological correlates of hepatitis C virus (HCV)-specific immunity are not well understood. Antibodies to HCV structural proteins do not appear to play a key role in clearance of the virus and do not persist after recovery. Here, we studied the kinetics of the cellular immune responses of three HCV-recovered chimpanzees during rechallenge with increasing doses of homologous HCV. Although HCV envelope

antibodies remained undetectable throughout the rechallenge, all animals mounted rapid HCV-specific T-cell responses. The pattern of the cellular immune response in blood and liver correlated with the virological outcome. The animal that most rapidly cleared circulating HCV as determined by nested reverse transcription-PCR (RT-PCR) displayed the most vigorous and sustained response of gamma interferon (IFN-gamma)-producing and proliferating CD4(+) T cells in the blood. Vigorous CD4(+) T-cell proliferation during viremia was followed by an increased frequency and a phenotypic and functional change of the tetramer(+) CD8(+) T-cell population. The second animal cleared HCV initially with strong peripheral and intrahepatic CD4(+) T-cell responses but experienced low-level HCV recrudescence 12 weeks later, when HCV-specific T cells became undetectable. The third animal maintained minute amounts of circulating HCV, detectable only by nested RT-PCR, in the face of a weak IFN-gamma(+) T-cell response. Collectively, the results suggest protective rather than sterilizing immunity after recovery from hepatitis C. The rate of HCV clearance following reexposure depends on the cellular immune response, the quality and quantity of which may vary among chimpanzees that recovered from HCV infection. PMID: 12663785 [PubMed - indexed for MEDLINE]

62: J Virol 2003 Apr;77(7):3950-61

Hepatitis C virus NS3 ATPases/helicases from different genotypes exhibit variations in enzymatic properties.

Lam AM, Keeney D, Eckert PQ, Frick DN.

Department of Biochemistry and Molecular Biology, New York Medical College, Valhalla, New York 10595, USA.

The NS3 ATPase/helicase was isolated and characterized from three different infectious clones of hepatitis C virus (HCV). One helicase was from a genotype that normally responds to therapy (Hel-2a), and the other two were from more resistant genotypes, 1a (Hel-1a) and 1b (Hel-1b). Although the differences among these helicases are generally minor, all three enzymes have distinct properties. Hel-1a is less selective for nucleoside triphosphates, Hel-1b hydrolyzes nucleoside triphosphates less rapidly, and Hel-2a unwinds DNA more rapidly and binds DNA more tightly than the other two enzymes. Unlike related proteins, different nucleic acid sequences stimulate ATP hydrolysis by HCV helicase at different maximum rates and with different apparent efficiencies. This nucleic acid stimulation profile is conserved among the enzymes, but it does not result entirely from differential DNA-binding affinities. Although the amino acid sequences of the three proteins differ by up to 15%, one variant amino acid that is critical for helicase action was identified. NS3 residue 450 is a threonine in Hel-1a and Hel-1b and is an isoleucine in Hel-2a. A mutant Hel-1a with an isoleucine substituted for threonine 450 unwinds DNA more rapidly and binds DNA more tightly than the parent protein. PMID: 12634355 [PubMed - indexed for MEDLINE]

63: JAMA 2003 Mar 12;289(10):1245-6

Hepatitis C virus and atherosclerosis in patients with type 2 diabetes.

Fukui M, Kitagawa Y, Nakamura N, Yoshikawa T.

Publication Types:

Letter

PMID: 12633185 [PubMed - indexed for MEDLINE]

64: Lancet 2003 Apr 12;361(9365):1301-2

Rapid spread of hepatitis C and needle exchange programme in Kolkata, India.

Sarkar K, Mitra S, Bal B, Chakraborty S, Bhattacharya SK.

Publication Types:

Letter

PMID: 12699985 [PubMed - indexed for MEDLINE]

65: Math Biosci 2003 Mar;182(1):1-25

Diseases with chronic stage in a population with varying size. Martcheva M, Castillo-Chavez C.

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mayam@duke.poly.edu

An epidemiological model of hepatitis C with a chronic infectious stage and variable population size is introduced. A non-structured baseline ODE model which supports exponential solutions is discussed. The normalized version where the unknown functions are the proportions of the susceptible, infected, and chronic individuals in the total population is analyzed. It is shown that sustained oscillations are not possible and the endemic proportions either approach the disease-free or an endemic equilibrium. The expanded model incorporates the chronic age of the individuals. Partial analysis of this age-structured model is carried out. The global asymptotic stability of the infection-free state is established as well as local asymptotic stability of the endemic non-uniform steady state distribution under some additional conditions. A numerical method for the chronic-age-structured model is introduced. It is shown that this numerical scheme is consistent and convergent of first order. Simulations based on the numerical method suggest that in the structured case the endemic equilibrium may be unstable and sustained oscillations are possible. Closer look at the reproduction number reveals that treatment strategies directed towards speeding up the transition from acute to chronic stage in effect contribute to the eradication of the disease.

PMID: 12547037 [PubMed - indexed for MEDLINE]

66: Med Lett Drugs Ther 2003 Mar 3;45(1151):19-20

Peginterferon alfa-2a (Pegasys) for chronic hepatitis C.

PMID: 12612502 [PubMed - indexed for MEDLINE]

67: Medicine (Baltimore) 2003 Mar;82(2):87-96

Severe autoimmune cytopenias in treatment-naïve hepatitis C virus infection: clinical description of 35 cases.

Ramos-Casals M, Garcia-Carrasco M, Lopez-Medrano F, Trejo O, Forns X, Lopez-Guillermo A, Munoz C, Ingelmo M, Font J.

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To determine the clinical characteristics and outcome of patients with chronic hepatitis C virus (HCV) infection presenting severe autoimmune cytopenia unrelated to interferon alpha therapy, we analyzed characteristics and outcomes of 35 patients with HCV (16 from our departments and 19 from the literature). We considered active autoimmune hemolytic anemia (AHA) as a decrease of at least 2 g/dL in hemoglobin levels, an increase of at least 0.6 mg/dL in the serum unconjugated bilirubin level, a reticulocyte count >5%, and a positive direct Coombs test. Severe neutropenia was defined as a neutrophil count <0.5 x 10(9)/L, and severe thrombocytopenia as a platelet count <30 x 10(9)/L. We identified the following cytopenias: AHA (17 cases), severe thrombocytopenia (16 cases), aplastic anemia (2 cases), severe neutropenia (1 case), refractory sideroblastic anemia (1 case), and pure red cell aplasia (1 case). Three patients simultaneously presented 2 types of severe cytopenias. Twenty-seven patients (77%) were female and 8 (23%) male, with a mean age at diagnosis of cytopenia of 51.7 years (range, 18-84 yr).

Immunologic markers were detected in 19 (68%) of 28 patients, the most frequent being hypocomplementemia in 16 (57%), cryoglobulins in 15 (54%), antinuclear antibodies in 12 (43%), and rheumatoid factor in 5 (18%). Other associated processes were autoimmune diseases in 14 (50%) of 28 and human

immunodeficiency virus (HIV) coinfection in 3 (9%) of 32. We found clinical and immunologic differences between HCV patients with AHA and those with severe thrombocytopenia. Patients with HCV-related AHA showed a higher prevalence of associated autoimmune diseases (71%), cryoglobulins (67%), and cirrhosis (59%). All had a good response to corticosteroids, but a poor prognosis (47% mortality). In contrast, patients with HCV-related severe thrombocytopenia had a lower prevalence of associated autoimmune diseases (11%), a poorer response to corticosteroids (55%), and lower mortality (6%), with HIV/HBV coinfections in some patients. The 35 cases presented demonstrate that different types of immune-mediated cytopenias may be severe and clinically significant in patients with HCV infection. Hemolytic anemia and severe thrombocytopenia were the most frequent cytopenias observed. Most patients responded well to corticosteroids, although a higher rate of mortality was observed in those with liver cirrhosis.

Publication Types:

Review

Review of Reported Cases

PMID: 12640185 [PubMed - indexed for MEDLINE]

68: MMWR Morb Mortal Wkly Rep 2003 Apr 4;52(13):273-4, 276

Hepatitis C virus transmission from an antibody-negative organ and tissue donor--United States, 2000-2002.

In June 2002, a physician reported to the Oregon Department of Human Services (DHS) a case of acute hepatitis C in a patient who had received a patellar tendon with bone allograft from a donor approximately 6 weeks before onset of illness. At the time of the donor's death in October 2000, his serum had no detectable antibody to hepatitis C virus (anti-HCV). The ensuing investigation conducted by CDC and DHS confirmed that the donor, although anti-HCV-negative, was HCV RNA-positive and the probable source of HCV infection for at least eight organ and tissue recipients. This report summarizes the preliminary results of the investigation. Although transmission from anti-HCV-negative tissue donors probably is rare, determining the frequency of transplantations from such donors and the risk for transmitting HCV to recipients is important in evaluating whether additional prevention measures are warranted.

PMID: 12729075 [PubMed - indexed for MEDLINE]

69: Mol Carcinog 2003 Mar;36(3):130-41

Hepatocyte growth factor, transforming growth factor alpha, and their receptors as combined markers of prognosis in hepatocellular carcinoma.

Daveau M, Scotte M, Francois A, Coulouarn C, Ros G, Tallet Y, Hiron M, Hellot MF, Salier JP.

INSERM Unite 519 and Institut Federatif de Recherches Multidisciplinaires sur les Peptides, Faculte de Medecine-Pharmacie, Rouen France.

A change in the balance between proliferation and apoptosis in the course of hepatocellular carcinoma (HCC) development and progression has been suspected. We wanted to identify related genes whose mRNA levels could provide markers of severity and prognosis after resection. The extent of cell apoptosis, proliferation, and differentiation was measured with a terminal deoxynucleotidyl transferase-mediated deoxyuridine 5-triphosphate-biotin nick-end labeling assay, and the Ki-67 index was determined in paired tumor and cirrhotic tissue samples from patients who had undergone HCC resection after diagnosis of hepatitis C-related or alcoholism-related cirrhosis. These patients included two groups with highly versus poorly differentiated tumor cells, and the latter was split into two subgroups of those with versus without early recurrence. The mRNA levels for various apoptosis-related or proliferation-related genes and those for the growth factor/receptor systems were measured by quantitative reverse transcriptase-polymerase chain reaction in paired tumor and

cirrhotic liver samples from every patient, and some of the corresponding proteins were detected by immunohistochemistry. In all instances, protein expression was highly heterogeneous within groups and similar between groups. In contrast, some differences in mRNA level between tumor and cirrhotic tissues were quite informative. Low levels of hepatocyte growth factor and transforming growth factor alpha mRNAs were found concomitantly in highly differentiated tumors, whereas overexpression of mRNAs for the cognate receptors c-met and epidermal growth factor receptor were found in poorly differentiated tumors and primarily in patients with early tumor recurrence. These results argue for growth factor-dependent HCC development and provide novel and combined prognosis markers after HCC surgery. Copyright 2003 Wiley-Liss, Inc.
PMID: 12619035 [PubMed - indexed for MEDLINE]

70: Radiology 2003 Mar;226(3):691-7

Coarse nodular US pattern in hepatic cirrhosis: risk for hepatocellular carcinoma. Caturelli E, Castellano L, Fusilli S, Palmentieri B, Niro GA, del Vecchio-Blanco C, Andriulli A, de Sio I.

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PURPOSE: To determine the prevalence of the coarse nodular ultrasonographic (US) pattern and its prognostic importance in terms of hepatocellular carcinoma (HCC) risk in hepatic cirrhosis caused by hepatitis B virus (HBV); HBV with hepatitis D virus (HDV), formerly known as hepatitis delta virus; hepatitis C virus (HCV); and alcoholic cirrhosis (ALC) or primary biliary disease (primary biliary cirrhosis [PBC]).

MATERIALS AND METHODS: Four hundred two cases of hepatic cirrhosis caused by HBV (94 patients), HDV (100 patients), HCV (100 patients), ALC (63 patients), or PBC (45 patients) were retrospectively reviewed to identify the US pattern present at diagnosis and its possible association with the cause of the disease and subsequent development of HCC during a mean follow-up of 43.9 months +/- 29.9 (SD). Data were analyzed with the chi2, Fisher exact, and log-rank tests and with the Kaplan-Meier method (all two-tailed). RESULTS: The coarse nodular pattern was found in a significantly higher percentage of patients with HDV-related cirrhosis (51%) compared with those with HBV (9%), HCV (9%), ALC (11%), or PBC (9%) (P <.001). This pattern was associated with a significantly increased risk for HCC in patients with cirrhosis and HBV-, HCV-, and ALC-related disease but not in those with HDV-related disease and PBC. CONCLUSION: The coarse nodular pattern is more often seen in patients with HDV-related cirrhosis, and, in this setting (in contrast to HBV-, HCV-, and ALC-related cirrhosis, as well as in PBC), it does not represent an added risk factor for HCC.

PMID: 12601208 [PubMed - indexed for MEDLINE]

71: Transfusion 2003 Apr;43(4):541-4

Fluctuation of HCV viral load before seroconversion in a healthy volunteer blood donor.

Fang CT, Tobler LH, Haesche C, Busch MP, Phelps B, Lepar G.

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BACKGROUND: Newly implemented NAT has been shown to be able to effectively identify HCV-positive blood donated during the preseroconversion period. STUDY DESIGN AND METHODS: EDTA-plasma pools of 24 donations were tested using an HIV-1/HCV multiplex NAT under an FDA-approved IND application. Samples in a positive pool were retested individually. Positive samples were further tested by two discriminatory assays to determine specific viral reactivity. Upon obtaining informed consent, seronegative donors with positive NAT results were enrolled into a follow-up

study for risk factor analysis and laboratory testing. RESULTS: A donation by a 29 year old female was identified as HCV NAT-positive with negative serology and an elevated ALT. Her two previous donations, 5 and 12 months earlier, were both seronegative and with normal ALT. Her husband tested positive for HCV RNA. The donor remained seronegative for at least 36 days. The index donation had a viral RNA concentration of >500,000 copies per mL while the first seropositive sample was NAT-negative. Laboratory data on serial follow-up samples showed 100- to 1,000-fold fluctuations in viral load during a period of 48 days prior to seroconversion. CONCLUSIONS: This case suggests that, at least in some newly infected individuals, the HCV viral load can fluctuate dramatically prior to seroconversion, and that NAT, even on individual samples, will not totally prevent HCV transmission.

PMID: 12662289 [PubMed - indexed for MEDLINE]

72: Transfusion 2003 Mar;43(3):418-9

Ten-year survival of transfusion recipients identified by hepatitis C lookback.

Vamvakas EC.

Publication Types:

Letter

PMID: 12675733 [PubMed - indexed for MEDLINE]

73: World J Gastroenterol 2003 Mar;9(3):505-8

Glucose intolerance in Chinese patients with chronic hepatitis C.

Chen LK, Hwang SJ, Tsai ST, Luo JC, Lee SD, Chang FY.

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AIM: To investigate the prevalence and the risk factors of glucose intolerance in Chinese patients with chronic hepatitis C and to evaluate the relationship between interferon (IFN) treatment and glucose intolerance in these patients. METHODS: Prospective cross-sectional study was done to evaluate the prevalence of glucose intolerance in Chinese patients with chronic hepatitis C virus (HCV) infection from the outpatient clinic of Department of Family Medicine, Taipei Veterans General Hospital. Chronic hepatitis C was defined as persistent presence of anti-HCV and persistent elevation of liver transaminase for at least 1.5 folds for at least 6 months. Moreover, patients were further categorized into normal fasting glucose and glucose intolerance (diabetes mellitus (DM) and impaired fasting glucose) according to the diagnostic criteria of American Diabetic Association. RESULTS: Totally, 359 Chinese patients with chronic hepatitis C were enrolled (212 males and 147 females, mean age=58.1+/-13.0 years). One hundred and twenty-three patients (34.3 %) had received various forms of IFN treatment. One hundred and twenty-five patients (34.6 %) had glucose intolerance, including 99 patients (27.6 %) with DM and 26 patients (7.0 %) with impaired fasting glucose. In comparison with those with normal fasting glucose levels, patients with chronic hepatitis C with glucose intolerance were significantly older, had a significantly higher body mass index, and they were more likely to suffer from obesity, to have family history of diabetes and to have had previous IFN treatment. Stepwise multivariate logistic regression revealed significantly that age \geq 57 years, obesity, previous history of IFN treatment and the presence of family history of diabetes were independent risk factors associated with the presence of glucose intolerance in chronic hepatitis C patients. CONCLUSION: In conclusion, 34.6 % of Chinese patients with chronic hepatitis C had glucose intolerance. Chronic hepatitis C patients who were older in age, obese, had previous IFN treatment history and had family history of diabetes were prone to develop glucose intolerance. To our knowledge, this is the first population-based report to confirm that interferon treatment to be an independent risk factor to develop glucose intolerance.

PMID: 12632506 [PubMed - indexed for MEDLINE]